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SOME PHARMACOKINETIC PARAMETERS OF DICLOFENAC IN RHEUMATOLOGICAL PATIENTS WITH DYSBIOSIS

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Resume.

The aim of the study was to study in a comparative aspect some of the pharmacokinetics of Diclofenac sodium in patients with rheumatoid arthritis with and without impaired gastric micro biocenosis (gastric dysbiosis). Materials and methods: 38 patients aged 18 to 60 years, with I-II-III degree of disease activity, were examined. In addition to the general clinical examination, an enzyme immunoassay and a urease test were performed to determine Helicobacter pylori and high-performance liquid chromatography to determine the pharmacokinetics of diclofenac. Results: the conducted studies and analysis of their results indicate that in conditions of rheumatoid arthritis, in particular, in the presence of comorbid conditions, there is a decrease in the metabolic rate and an elongation of the half-life of nonsteroidal anti-inflammatory drugs, which increases the risk of side effects, especially from the gastrointestinal tract and significantly affects the course of the disease and treatment results.

Key words

Rheumatoid arthritis, diclofenac, high-performance liquid chromatography, pharmacokinetics.

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Summary. The aim of the study was to study in a comparative aspect some of the pharmacokinetics of Diclofenac sodium in patients with rheumatoid arthritis with impaired gastric micro biocenosis (gastric dysbiosis) and without disturbance (without dysbiosis). Material and methods: We examined 38 patients aged 18 to 60 years, with I-II-III degree of disease activity. In addition to general clinical examination, an enzyme-linked immunosorbent assay and a urease test were performed to determine Helicobacter pylori and high-performance liquid chromatography to determine the pharmacokinetics of diclofenac. Results: studies and analysis of their results indicate that in conditions of rheumatoid arthritis, in particular, in the presence of comorbid conditions, there is a decrease in the metabolic rate and lengthening the half-life of NSAIDs, which increases the risk of side effects, especially from the gastrointestinal tract and significantly affects the course of the disease and treatment results.

Currently, much attention is being paid to conducting pharmacokinetic (FC) studies to study the processes of intake, distribution, biotransformation and excretion of medicinal substances, as well as to identify links between the concentration of a medicinal substance and (or) its metabolites in biological fluids and tissues and the pharmacological effect. Clinical pharmacokinetics determines which dosage of medicinal substances ensures their necessary concentration in the body's environment to achieve an optimal therapeutic effect. Currently, several methods are known for the determination of diclofenac in biological fluids: potentiometric analysis [1], high performance liquid chromatography (HPLC) [3], capillary zone electrophoresis [7], spectrofluorimetry [8], thin-layer chromatography [9], polarographic analysis [4].

It is well known that in the treatment of rheumatoid arthritis (RA), nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used as symptomatic therapy, of which diclofenac sodium (DN) is the most commonly used. The duration of the anti-inflammatory effect and the effectiveness of NSAIDs in general are directly dependent on the level of effective drug concentration and the duration of their free-form circulation in the blood. In clinical practice, these parameters are determined by a number of pharmacokinetic parameters, in particular Cal (elimination constant), Cl (clearance of the drug), T1/2 (half-life of the drug), etc. In the human body, diclofenac undergoes biotransformation under the influence of the cytochrome P450 enzyme system to form three primary metabolites: 3-hydroxydiclofenac, 4-hydroxydiclofenac, and 5-hydroxydiclofenac. The primary metabolites conjugate to form two secondary ones, 4,5-dihydroxy-diclofenac and Z-hydroxy-4-methoxy clofenac (3,4-HMD). All metabolites are significantly inferior to the original drug in terms of therapeutic activity. The half-life of diclofenac sodium

and four of its five main metabolites ranges on average from 1 to 3 hours, but for 3,4-HMG it reaches 80 hours. DN does not accumulate with prolonged use, all its metabolites are excreted in urine and bile. 95.7% of the drug binds to whey proteins [1]. According to the results of previous studies, the concentration of diclofenac sodium reached a maximum after intramuscular administration after 15 and 25 minutes [2, 6]. In addition, it should be noted that most NSAIDs belong to the category of drugs that are metabolized in the liver, which makes the problem of studying their metabolism in the body particularly relevant in practical terms.

Rheumatoid arthritis is often accompanied by visceral manifestations from other organs and systems, as well as concomitant diseases (comorbid conditions) [5], which can affect the pharmacokinetic parameters of NSAIDs used.

Aim of the study

Aim was to study in a comparative aspect some of the pharmacokinetics of Diclofenac sodium in patients with rheumatoid arthritis with impaired gastric micro biocenosis (gastric dysbiosis) and without impaired gastric micro biocenosis (without dysbiosis).

Materials and methods.

38 patients with reliably established RA aged 18-60 years, with a disease duration of more than 5 years. RA patients were divided into 3 groups: RA patients without dysbiosis - 28.6%, RA patients with dysbiosis -42.8%, RA patients with dysbiosis and H.pylori - 28.6%.

The method of high performance liquid chromatography (HPLC) with mass spectrometric (MS) detection was used to determine diclofenac in blood plasma. The Agilent 6420 ultra-high-performance liquid chromatography (HPLC) with a triple quadrupole mass spectrometer from agilent technologies (USA) was used in the work. HPLC pure acetonitrile was purchased from Sigma-AldrichTradingCo (Schnelldorf, Germany). Ultrapure water was obtained using a water purification system from Sartorius Labinstructs Gmbh Co. KG (Göttingen, Germany). All other chemicals were analytically pure and used without additional purification.

Sample preparation. Control blood samples were taken from patients after taking diclofenac tablets (50 mg) (positive control) after 0.5, 6 and 12 hours. Blood samples were centrifuged at 2000 rpm for 6 minutes. After that, the blood plasma was injected into the HPLC column for analysis.

To prepare standard diclofenac samples, the substrate was dried, the exact amount was weighed, and a basic aqueous solution was prepared at a concentration of 1 mg/ml. Samples with different concentrations of diclofenac were prepared from this solution for both qualitative and quantitative analysis.

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HPLC-MS/MS screening. HPLC analyses were performed with 1 µl samples, which were injected using an automatic sampler. As the mobile phase, either only water acidified with 0.01% formic acid was used, or acetonitrile – water added 0.01% formic acid for positive ion control at a flow rate of 0.2 ml/min.

The analyses were performed in full scan mode (Full Scan Mode) to determine the chemical composition of the plant. Qualitative and quantitative analysis of diclofenac. Standard diclofenac solutions were freshly prepared by diluting the basic solution (1 mg/ml) in ultrapure water. Samples ranging from 0.01 to 1000 ng/µl were prepared for quantitative analysis for calibration, detection limit (PO) and quantification limit (MPR). These solutions were stored at +4 ° C before analysis. PO and PCO were determined experimentally from the signal-to-noise ratio by diluting the basic concentration (1 mg/ml)

The results and their discussion.

The results of these studies are shown in Figures 1,2,3. As can be seen from the data presented in Figure 1, in patients with rheumatoid arthritis without dysbiosis in the stomach, Cal is reduced by 34.4% compared with the control indicator. At the same time, in patients with rheumatoid arthritis with gastric dysbiosis, this indicator is reduced to a greater extent (almost 1.5 times compared with the control). If we consider that this indicator of pharmacokinetics reflects the rate of elimination of the drug from the body, it becomes obvious that in conditions of rheumatoid arthritis, the rate of elimination of the studied drug from the patient's body slows down. And with the addition of dysbiosis in the stomach, this process is even more aggravated.

It is well known that the rate of elimination of xenobiotics, including drugs metabolized in the liver, primarily depends on the rate of their biotransformation (metabolism) in the body. In this regard, we studied the Cl indicator, which reflects the degree of purification of the body from the drug. An analysis of the results of this indicator also indicates a significant suppression of this body function in conditions of rheumatoid arthritis, especially in conditions of comorbid conditions (Fig.2).

Suppression of drug metabolism in the body and a decrease in the rate of their excretion from the body is accompanied by the accumulation of the applied drug in the blood. Indeed, as can be seen from the data presented in the figure, in patients with rheumatoid arthritis, the T1/2 value is 1.5 times longer than in the control. And in the conditions of the appearance of dysbiosis of the stomach by almost 2 times, respectively (Fig. 3).

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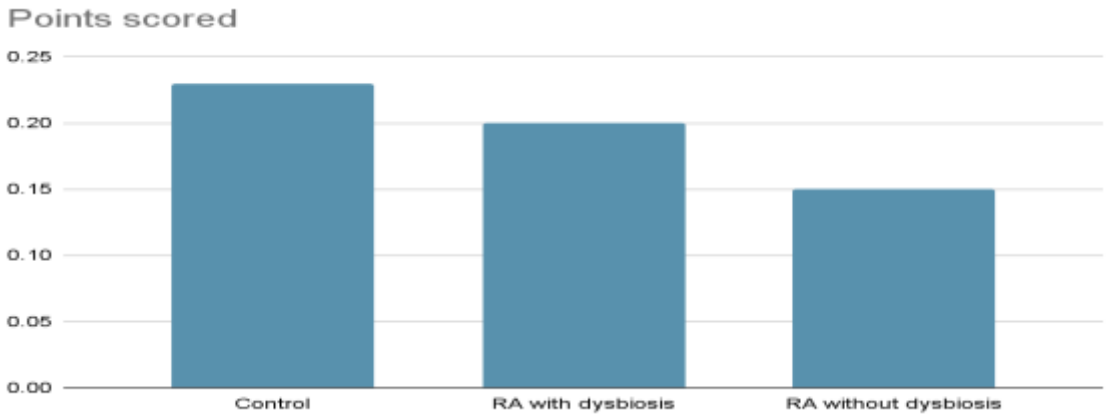

Fig. 1. Pharmacokinetic parameters of diclofenac sodium in patients with rheumatoid arthritis: A is an indicator of the elimination constant (Cal)

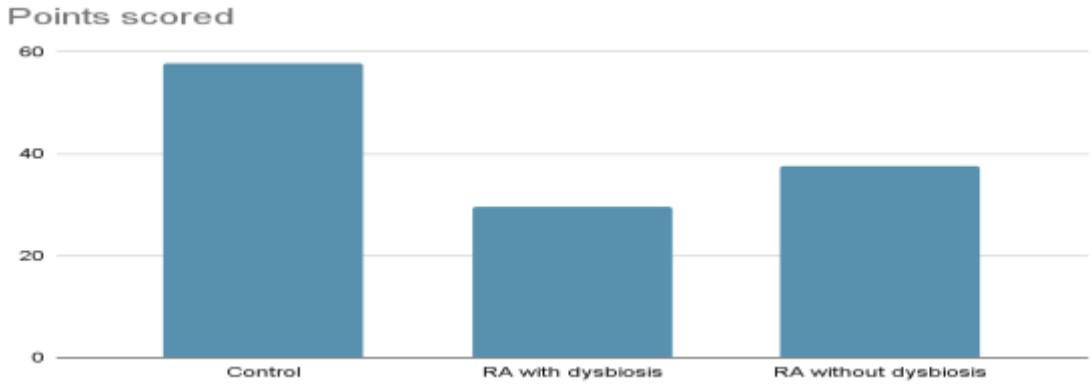

Fig. 2. Pharmacokinetic parameters of diclofenac sodium in patients with rheumatoid arthritis: B-clearance of the drug (Cl)

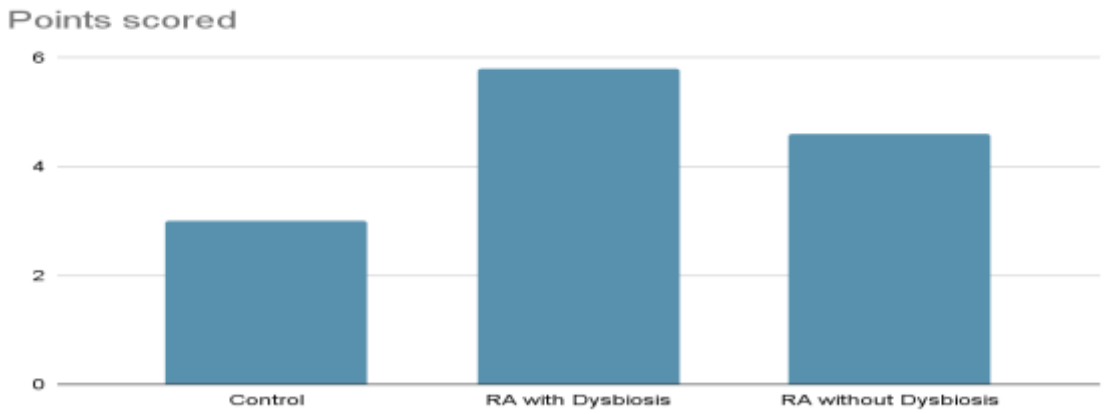

Fig. 3. Pharmacokinetic parameters of diclofenac sodium in patients with rheumatoid arthritis: B-half-life period (T1/2).

The following is an example of calculating pharmacokinetic parameters in a patient with RA (Fig. 4)

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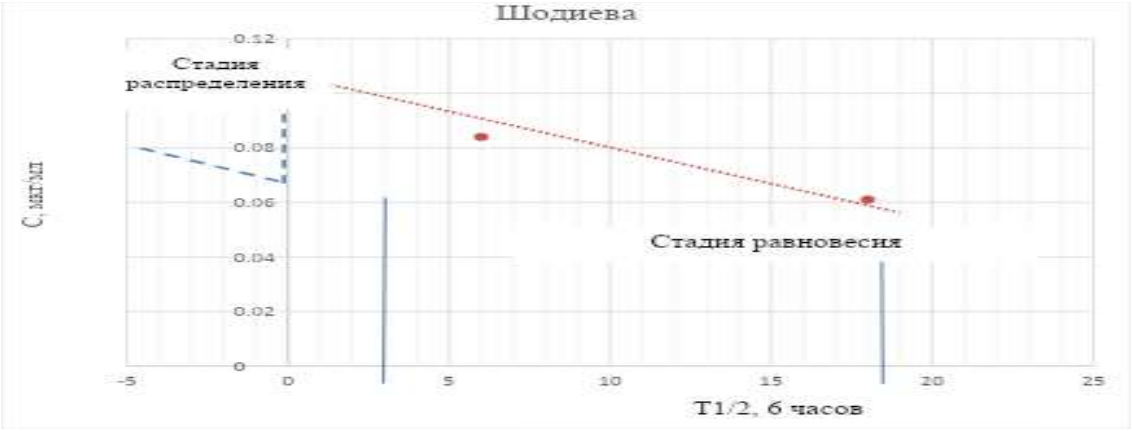

V_p = Dose /C_0 = 25 mg / 0.1 = 250 L
K_{el} = 0.693/$T_{1/2}$ = 0.693 / 6 Time = 0.1155 h^{-1}
Cl = $V_p \times K_{el}$ = 250 L×0.1155 h^{-1} = 28.875 l/h
Diclofenac is normally released after 2-3 hours. Let's say if it's 2.5 hours, then
K_{el} (norm) = 0.693/$T_{1/2}$ = 0.693/2.5 hour = 0.2772 h^{-1} $K_{el} < K_{el}$ (norm)
Cl (norm) = $V_p \times K_{el}$ = 250 l×0.2772 h^{-1} = 69.3 l/h Cl < Cl (norm)

Therefore, in patients with rheumatoid arthritis, a significant prolongation of the half-life of the studied drug is observed. Moreover, the presence of comorbid conditions further extends this parameter, increasing the risk of adverse effects.

Based on the obtained pharmacokinetic data, two possible strategies can be considered to reduce the side effects of NSAIDs:

1. Reducing the NSAID dosage while maintaining the same dosing intervals; or
2. Extending the dosing intervals without altering the drug dosage, thereby reducing the frequency of administration.

Additionally, to protect the gastric mucosa, the treatment regimen should include antacids, proton pump inhibitors, M-cholinergic receptor blockers, and H2-histamine receptor antagonists.

In light of these considerations, we also examined and analyzed the structure and frequency of adverse effects associated with NSAID therapy in the studied patient groups. The results of this analysis are presented in Table 1.

Table 1. Structure and Frequency of NSAID-Related Adverse Effects in Patients with Rheumatoid Arthritis

Gastro-Duodenal Lesions	Patient Groups

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	RA without Dysbiosis	RA with Dysbiosis	RA with Dysbiosis and *H. pylori*
Heartburn (%)	50	58	80
Belching (%)	18	33	12
Epigastric Heaviness (%)	12	42	50
Epigastric Pain (%)	58	54	68
Constipation (%)	-	14	4
Poor Appetite (%)	10	15	18
Esophagitis (%)	77	50	88
Gastric and Duodenal Ulcers (%)	10	25	28

As evident from the presented data, the frequency of the most characteristic adverse effects is significantly higher in the group of patients with rheumatoid arthritis and gastric dysbiosis compared to those without gastric dysbiosis. Specifically, symptoms such as heartburn, epigastric heaviness, and epigastric pain are increased by 38%, 19%, and 26%, respectively, in patients with rheumatoid arthritis and gastric dysbiosis. Additionally, these patients exhibit a relatively higher incidence of esophagitis and peptic ulcers of the stomach and duodenum.

Thus, in the presence of rheumatoid arthritis with comorbid conditions, NSAID-related adverse effects are more frequently observed.

The conducted studies and the analysis of their results indicate that in rheumatoid arthritis, particularly in the presence of comorbid conditions, significant shifts occur in the pharmacokinetic parameters of NSAIDs. The reduced metabolic rate and prolonged half-life of NSAIDs increase the risk of adverse effects, particularly affecting the gastrointestinal tract, which significantly impacts disease progression and treatment outcomes. This finding underscores the necessity of considering these results when managing this pathology and developing a personalized approach to the treatment of rheumatoid arthritis.

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